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Review Article

Gender - based Research and Women in Clinical Trials: Improving Women's Health Care

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Abstract

Routinely, research is done on animals and human beings. But both animals and human beings include two species- the male and the female. It is known that there are differences between the two entities in several aspects including the genes, the hormones, the anatomy, the physiology, the pharmacological processes, interactions between the genes and the whole body, lifestyle, environment and behavior. That means, gender- specific clinical research which takes into consideration these differences is very important; nevertheless, there exist several gaps in women's health due to problems in conducting gender-specific research and issues regarding the participation of women in clinical trials. What is the current status of gender-based research and women in clinical trials? Are there research gaps in women's health? Can gender- specific research contribute to improving women's health? We did a literature search to find answers to these interrelated questions. We found that currently, data on gender differences in response to clinical interventions is limited. We conclude that sex-specific reporting, documentation and analysis of research and inclusion of women as study participants in clinical trials is important and can improve the value of research. This can contribute to improving women's health.

Keywords: Clinical trials; Drugs; Gender; Interventions; Pharmacology; Sex; Women's health

Article Proper

We may add that it is not an act of justice but of foolish injustice to pretend the sexes are the same.'

J. Budziszewski

Introduction

Men and women differ in various ways and there are several differences other than the commonly thought of differences in anatomy and hormones. These include complex and diverse interactions between the genes and the whole body [1]. Although there are life styles, environmental and behavioral differences, there are biological differences at the molecular and cellular level between men and women [2]. Are these differences taken into consideration in clinical research? What is the current global status of sex- based research? Are men and women equally included and represented in peri-operative clinical trials and clinical research? Are there research gaps in women's health? Can the promotion of gender- specific research improve women's health care? Keeping these questions in mind, we did a literature search for the words 'sex- based research', 'sex and gender', 'women and clinical trials', 'gender- based studies', 'sex and gender differences in anesthesia' using PubMed, Embase, Cochrane and Google Scholar for all manuscripts published till September 2020. Cross references were searched for from the primary manuscripts. We followed the PICOS (Population, Intervention, Control, Outcomes, Study type) strategy to formulate and also answer our research question. The information thereby collected is presented in this article. This review includes 41 manuscripts inclusive of various types of publication manuscripts (review articles, editorials, committee recommendations, research studies, e-books and textbooks of anesthesia) in relation to our research question.

Sex and Gender Differences and their Clinical and Perioperative Implications

Physiological and pharmacological differences exist between men and women. Men and women have a difference in composition of the body which includes fat composition, waist circumference, Body Mass Index (BMI) and extracellular fluid volume. There are sex differences in physiology in terms of body fat, metabolic rate, muscle mass, total body weight, cardiac mass, Left Ventricular Ejection Fraction (LVEF), diastolic function, stroke volume, blood pressure, resting heart rate, ventilatory response to hypoxia/ hypercapnia, apnoeic threshold, expiratory flow rates, pain threshold, thermal response and plasma rennin activity.

The response to drug treatment is different in males and females because they differ in their pharmacokinetics and pharmacodynamics. Endogenous hormones like estradiol and testosterone, can have different levels in the circulation and these can have an effect on pharmacodynamics and pharmacokinetic parameters. Pharmacokinetics include bioavailability, volume of drug distribution, protein binding, drug metabolism and renal clearance [3]. The relative adipose tissue percentage irrespective of the body mass index, the reproductive physiology and special situations like pregnancy and lactation can contribute to differences in male and female pharmacokinetics and dynamics [4]. A majority of the lipid soluble drugs have a potential to produce temporary reservoirs as seen with thiopentone. The factors that influence this characteristic are relative lipid solubility, amount of adipose tissue in the body and

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volume of distribution of the drug; Women have a higher percentage of their total body weight as fat compared to men and this percentage increases as age advances in both. Slowly metabolized toxicants that are lipid soluble are produced more in women, mainly those who are pregnant because of a larger proportion of body fat; Nevertheless, the volume of distribution of thiopentone is slightly larger in females, causing a longer elimination half-life [5]. Neuromuscular blockers like vecuronium and rocuronium have a faster onset of action and prolonged duration in women because of differences in organ blood flow and body fat [6,7]. Ordinarily, men have greater total body water including extracellular and intracellular water, total blood volume including plasma volume and red blood cell volume than women. Hence, when the same dose of a water soluble drug when exposed to an average male and female, there will be a difference in its volume of distribution and a decrease in its concentration [8]. Generally, water-soluble drugs, such as muscle relaxants, have a lower distribution volume in women [9]. However, the volume of distribution of lipid soluble drugs like propofol, opioids and benzodiazepines is larger in women than in men [7]. The volume of distribution and clearance rate for propofol is larger and higher in women, but both males and females have a similar elimination half-life [10]. Some studies have found that the calculated plasma concentration of propofol was significantly more and the effect site concentration (EC50) for propofol was higher in males than in females, thus showing that males require more propofol than women for anesthetic induction [11,12]. It is observed that when premedicant drugs and drugs for postoperative analgesia are administered in fixed dosages (mg) instead of as per body weight (mg/kg) or body surface area (mg/m2), sex gender differences in distribution volumes occur [13]. The differences in biotransformation of certain drugs like heparin, acetylsalicylic acid and benzodiazepines like chlordiazepoxide and flurazepam are sex-dependant [14]. The safety or efficacy of prescription products are different in men and women because of differences in pharmacology of the specific drugs including mainly pharmacodynamics and pharmacokinetics and varying responses to drugs [15,16]. E.g., Zolpidem is a drug that has dosing based on sex. Women have a higher risk of experiencing negative effects from drug treatments. It is likely that respiratory depression and other adverse effects will occur more easily in women when administered the same dose as males. Males are less sensitive than females to opioid receptor agonists. Drugs which prolong the QT interval e.g., volatile anesthetics can produce cardiac arrhythmias like torsades de pointes in women more easily [15,16], and this may result in severe cardiac arrhythmias. It has also been described that both intravenous and volatile anesthetics may cause greater decrease in blood pressure, with reflex increase in heart rate in women than in men [17]. The occurrence of acute liver failure due to certain drug exposures has been observed more in women than in men [15]. The difference in pharmacokinetics can account for women having a faster speed of awakening due to less sensitivity to hypnotic effect of drugs, more chances of intra operative awareness, more peri operative sequelae like anaphylactic and anaphylactoid reactions, postoperative nausea and vomiting, sore throat, headache, backache and higher pain scores following anesthesia [3]. Ketamine induced emergence delirium is seen more in women than in men [18]. The incidence of allergic reactions in anesthesia (especially due to neuromuscular relaxants) is more in women (70% in women versus 30% in men). Succinylcholine produces more adverse drug reactions in women and atracurium produces more adverse drug effects in men [19]. Rocuronium produces more pain on injection in women than in men [20]. Local anesthetics have not yet exhibited any sex based variations in their efficacy [21]. However, the distribution volume of lidocaine is more in women than in men; nevertheless, the incidence of local anesthetic induced adverse effects is more in women than in men [9,22].

Gender can shape patient's experiences in the peri operative period starting from the preoperative period up to patient discharge and can influence patient care and outcomes in the peri operative period. Gender may come into play peri operatively and lead to biases in preoperative examination and testing [23]. There are differences in how diseases present in males and females e.g., women with cardio-vascular diseases may experience differences in signs and symptoms [24]. A study found that during preoperative Cardio Pulmonary Exercise Testing (CPET), males had a higher oxygen consumption at peak exercise and anaerobic threshold both before and after correction for body weight [25]. This means that there are sex based differences in the assessment of CP fitness during the surgical risk assessment. Gender differences in cardiovascular responses to psychological stress exist with greater responses of SBP and DBP in male and those of HR in females [26]. It is said that we should pay special attention to transgenders in peri operative care because the health risks and healthcare needs cum disparities are special in them [27].

Peri operative outcomes may be different for men and women. The female sex has been shown to be associated with a worse outcome in terms of morbidity and mortality, increased length of hospital stay and decreased functional outcome following some types of surgery [28]. Sex of the organ donor and recipient impacts graft survival and mortality [23]. Men and women differ in their biological responses to diseases like stroke, sepsis, myocardial infarction and trauma [1]. A cohort study including 600 men and 600 women examining the relationship between gender and adverse effects after spinal anesthesia with lidocaine found that there were significant differences between the incidence of complications like nausea, vomiting, headache, urinary retention and backache [29].

Differences between the Terms 'Sex' and 'Gender'

Many researchers, physicians and trainees do not really know the differences between the terms 'sex' and 'gender'. The situation at present is such that gender or sex is defined in only a few randomized controlled trials while describing demographic characteristics of the study population. The meaning of these two terms varies among various studies because they are many times used equivalently. Leslie and colleagues found that 9.3% of the papers in international journals related to anesthesiology reported both sex and gender and that in approximately ninety percent of the articles, the terms 'gender' and 'sex' were used in an interchangeable manner. Nevertheless this kind of reporting is not correct and should not be used [30,31]. There are differences between the two terms and the terms should be used carefully.

'Sex' is a biological state whereas 'gender' is a set of attitudes, feelings and behaviors. 'Sex' is defined by chromosomes, gonads, genitals and sexual characteristics. 'Gender' is linked to a person's identity as a man or woman [32].

What is the Importance of Sex-Specific and Gender Specific Research and How to do it?

Inclusion of sex, gender in medical research and in peri operative clinical trials to detect gender differences in the effect of pharmaceutical and non-pharmaceutical interventions is very important [33]. Sex-

gender specific analyses in research can improve the value of research. In fact, the International Council of Medical Journal Editors (ICMJE) requires that the terms 'sex' and 'gender' should be used correctly by authors, the sex and gender of the study participants, the sex of animals or cells should be reported and also that the methods used to determine sex and gender should be described unless deemed to be inappropriate [34].

However, there is a broad, persistent problem in all scientific fields: a lack of sex-specific research and a smaller number of female research participants, skewing results towards male-specific outcomes and subsequent clinical practice [2,25]. It is said that the conclusions about data on sex differences are limited because they are mostly obtained by post hoc analysis [8]. In a study on articles published in eight international anesthesia journals, it was found that in 2016, both male and female participants were reported in only 42% of original research papers and no papers reported participants from the transgender. This shows that gender bias may be persist in medical research. The study showed that authors of study participants have not put into practice the ICMJE recommendations regarding appropriate use of the terms 'gender' and 'sex'. The authors recommend that the numbers and percentages of both male and female patients and other sexes/genders should be reported appropriately [30]. Wide research gaps can result in the gender minority populations if reporting of intersex or transgender participants is not done [27,31]. Documentation of sex and gender of the patient by the patient, family, friends, referring doctor, administration clerk, hospital doctor, dispatcher and paramedic during elective referral/emergency department presentation/ambulance retrieval is recommended to improve sex documentation in medical records. This can help researchers later on. Researchers can face several problems while designing trials in a manner conducive to do a sex analysis of their observations and results [35]. The problems include the following:

1. The sample size should be large enough to have a sufficient power for subgroup analyses; but difficulties may be encountered in the estimation and recruitment of such a sample. Sample size can be a primary issue in breaking down data by sex. Two studies with adequate power and one in each sex or a single adequately powered study capable of detecting interaction may be needed.
2. Reproductive endocrinology will be variable in test subjects.
3. The hormonal/menopausal status of females in a study and contraceptive use in them can affect drug pharmacokinetics and dynamics and thereby their allocation in the study [36].
4. Lack of knowledge of statistical tests/methods to analyze differences between sexes.

Some researchers have suggested rules which can help other researchers to design trials that have a sex-gender approach [37]:

1. Researchers should define terminology for sex or gender in clinical protocols.
2. Research teams should receive training in such a way that investigator sex-gender bias is avoided.
3. The whole human life-span should be considered for appropriate inclusion of gender/sex as a basic variable in randomized controlled trials.
4. A detailed patient history including psychosocial and biological aspects is needed to understand the interactions among biological aspects and environmental ones.
5. Pretreatment response to placebo should be the basis of selecting study participants whenever an attempt is made to evaluate the response to placebo in man and woman.
6. One should know how sex-gender and hormones can affect biomarkers.
7. Even if sex-gender analysis does not yield sex- gender differences, those who conduct research trials trial should remember that reporting of the absence of sex gender differences is very important.
8. Members of Research Ethics Committees can enrich their knowledge on matters like how sex-gender issues can be included when designing and conducting clinical studies.
9. A good alliance between the patients, researchers, health care providers and pharmaceutical industry can ensure biomedical research that is sex-gender sensitive.
10. Scientific journals by keeping sex- gender analysis as a journal requirements can play an important role.

Participation of Women in Clinical Trials

Though sex and gender- specific research is important, women's representation in clinical trials has always been deficient as per history. In the previous years, the consideration and inclusion of men have overshadowed women in the design and conduct of clinical research. The observer bias in assuming the attitude of a male in conducting trials was a factor contributing to this. Also, many a times, researchers thought that woman and men would have a similar response from drugs in clinical trials. The fluctuating level of hormones made women to be viewed as expensive and confounding test subjects [2,24]. Social barriers that could discourage women from participating in clinical trials include inability of the women to return for follow-up visits because of lack of time and also problems in commuting and transport. Nonetheless, the Indian Council of Medical Research (ICMR) 2017 guidelines state that women have equal right to participate in the trials; however their informed consent is mandatory as like in others. This is sometimes difficult to obtain due to cultural restrictions and this in turn may reduce their participation in trials. Sometimes their educational and socioeconomic status may interfere with their participation. They are considered to be having more than minimum risk when participating in clinical trials [38].

Policies and guidelines that consider pregnant woman as a "vulnerable population" have come into being due to concerns of potential adverse effects on reproduction. These led to pregnant and lactating women and women with poor access to health care being excluded from research. The policies also produced a restriction in the ability of women with child bearing potential to enroll in clinical trials; Nonetheless, it is speculated that general anesthetic agents can affect embryo development, reproductive outcomes and in vitro fertilization outcomes. Currently, they have been classified as a vulnerable population in ICMR 2017 ethics guidelines in line with ICH-GCP guidelines, which mandates that their representation in trials at levels up to Phase 2 and Phase 3 needs strong scientific necessity (like drugs used in women/pregnancy/lactating mothers). Hence naturally, up to that level, their recruitment is limited and not restricted. Whenever a researcher plans research on a vulnerable population like this, it is a rule that others will be responsible for the

protection of their interests. They have an equal right as others to be included as research subjects and they should be solely recruited for research if research should answer their health needs [38].

While there are several reports that suggest women underrepresented in clinical trials especially cancer, vascular surgery, hepatic, digestive, chronic kidney disease and cardiovascular trials, some studies assert that they enjoy equal access to trials [39]. It is also said that women are over represented in topics related to musculoskeletal and neurological topics.

A recent cross-sectional study into publicly available FDA approved frequently prescribed drugs found that out of 185479 trial participants, 47% were female and 44% were male. Thus, there was no evidence that women have been systematic under-represented in clinical trials. However, there was a variation in the number of female participants according to the phase of the trial, such that 22% females participated in phase I trials, 48% in phase II and 49% in phase III trials [40].

A survey by the FDA center for drug evaluation and research for new drugs approved between 2013 and 2015 to study the demographics of participants in clinical trials and the presence of efficacy and safety analysis by sex showed that for most new drugs there was appropriate sex participation when the estimated disease prevalence by sex was considered [41].

Efforts to Promote Women's Health Research

In several countries, remarkable advances in policies have been made to ensure and help the increase in participation of women in research studies [39]. Several organizations in the world are trying to promote research in women's health. The Society for Women's Health Research (SWHR) in Washington is a strong promoter of improvement in women's health through science, policy and education. It is a strong advocate of research on biological sex differences in disease [42]. In 2017, for the first time, in the US Food and Drug Administration (FDA) drug trials, women accounted for over half of research participants for approved drugs. All this was possible because of strong and constant advocacy done for this by the SWHR. Several journals ask authors to conduct subgroup analyses by sex.

Conclusion

We conclude that there is a need to understand the clinical implications of the differences in the biology and physiology of men and women. Sex specific reporting, documentation and analysis of research and inclusion of women as study participants in preclinical and clinical trials is important and can improve the value of research. Currently, data on gender differences in response to clinical interventions is limited and there is a need for more research in the area of gender differences in response to clinical and pharmaceutical interventions, and women -specific health research including peri operative medicine related research. All this can reduce the research gaps in women's health and go a long way in improving women's health care.

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